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(54) DIAMINO-TETRAHYDRO-BENZTHIAZOLES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(54) דיאמינו-טטראהידרו-בנזתיאזולים, הכנתם ותכשירי רוקחות המכילים אותם

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דיאמינו-טטראהידרו-בנזתיאזולים, הכנתם ותכשירי רוקחות
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Diamino-tetrahydro-benzthiazoles, their preparation and pharmaceutical compositions containing them

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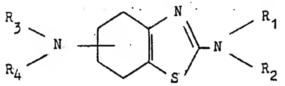
Chemical Compounds

The present invention relates to tetrahydrobenzthiazoles, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention, there are provided compounds of general formula I



(I)

[wherein

R_1 represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

R_2 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

R_3 represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms) and R_4 represents

a hydrogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or R_3 and R_4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group] and acid addition salts thereof.

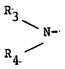
Where the compound of formula I is a compound possessing a chiral centre, the invention extends to all possible isomers of the compound in question.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable acid addition salts, but other acid addition salts may find use, for example in the preparation of compounds of general formula I and physiologically acceptable acid addition salts thereof. The expression "acid addition salts" as used herein includes salts formed with inorganic or organic acids.

The compounds of general formula I possess interesting pharmacological properties, and in general show an effect on the central nervous system and/or the circulation.

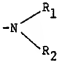
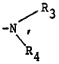
If in general formula I one of the groups R_1 and R_3 represents an acyl group or both of R_1 and R_3 represent acyl groups, these compounds of general formula I are valuable intermediate products for preparing other compounds of general formula I.

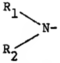
Preferred compounds of general formula I above are those wherein the group



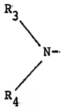
is in the 5 or 6-position.

As examples of the definitions of the groups

 and 

the 

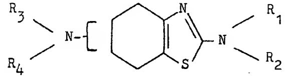
group may represent an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, N-methyl-allylamino, N-ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-allylamino, propargylamino, N-methyl-propargylamino, N-n-propyl-propargylamino, formylamino, acetylamino, propionylamino, butanoylamino, hexanoylamino, N-methyl-acetylamino, N-allyl-acetylamino, N-propargyl-acetylamino, benzylamino, N-methyl-benzylamino, 2-chloro-benzylamino, 4-chloro-benzylamino, 4-fluoro-benzylamino, 3,4-dichloro-benzylamino, 1-phenylethylamino, 2-phenylethylamino, 3-phenyl-n-propylamino, benzoylamino phenacetylamino or 2-phenylpropionylamino group; and

the 

group may represent an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, n-heptylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino,

methyl-n-propylamino, methyl-isopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, diallylamino, N-methyl-allylamino, N-ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-allylamino, propargylamino, butin-2-ylamino, hexin-2-ylamino, dipropargylamino, N-methyl-propargylamino, N-ethyl-propargylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, N-methyl cyclohexylamino, N-ethyl-cyclohexylamino, formylamino, acetylamino, propionylamino, butanoylamino, pentanoylamino, hexanoylamino, heptanoylamino, N-methyl-acetylamino, N-ethyl-acetylamino, N-n-propyl-acetylamino, N-allyl-acetylamino, benzoylamino, fluorobenzoylamino, chlorobenzoylamino, bromobenzoylamino, phenylacetamino, 2-phenylpropionylamino, N-methyl-benzoylamino, N-ethyl-chlorobenzoylamino, Dichlorobenzoyl-amino, N-cyclohexyl-acetylamino, benzylamino, chloro-benzylamino, bromobenzylamino, 1-phenylethylamino, 2-phenylethylamino, 2-phenyl-n-propylamino, 3-phenyl-n-propylamino, N-methyl-benzylamino, N-ethyl-benzylamino, N-ethyl-chlorobenzylamino, N-ethyl-2-phenylethylamino, N-acetyl-benzylamino, N-acetyl-chlorobenzylamino, N-allyl-benzylamino, N-allyl-chlorobenzylamino, pyrrolidino, piperidino, hexamethyleneimino or morpholino group.

Particularly preferred compounds of general formula I are, however, the compounds of general formula Ia



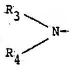
(Ia)

(wherein

R_1 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichloro-benzyl or phenylethyl group;

R_2 represents a hydrogen atom or a methyl or ethyl group; and

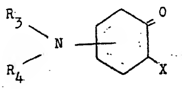
R_3 represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms or an allyl, propargyl, benzyl, chlorobenzyl, phenylethyl, cyclopentyl or cyclohexyl group and R_4 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl group; or R_3 and R_4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group) and especially the compounds wherein the group



is in the 6-position, and acid addition salts thereof.

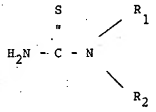
The new compounds may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

a) Reaction of a cyclohexanone of general formula II



(II)

[wherein R_3 and R_4 are as hereinbefore defined; and X represents a nucleophilic leaving group such as a halogen atom (e.g. a chlorine or bromine atom)] with a thiourea of general formula III

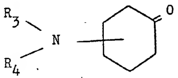


(III)

(wherein R_1 and R_2 are as hereinbefore defined).

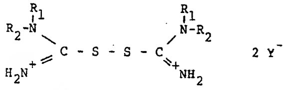
The reaction is carried out in the melt or in the presence of a solvent or mixture of solvents (such as, for example, water, ethanol, water/ethanol, pyridine, dioxan, dioxan/water, glacial acetic acid, tetrahydrofuran or dimethylformamide) conveniently at temperatures of between 0 and 150°C, but preferably at temperatures of between 20 and 100°C, and optionally in the presence of a base (e.g. sodium hydroxide solution, sodium acetate, pyridine, triethylamine or N-ethyl-diisopropylamine). The compounds of general formula II used as starting materials need not be isolated.

b) Reaction of a compound of general formula IV



(IV)

(wherein R_3 and R_4 are as hereinbefore defined) with a formamidine disulphide of general formula V



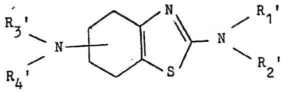
(V)

(wherein R_1 and R_2 are as hereinbefore defined; and Y^- represents an anion of an inorganic or organic acid).

The reaction is preferably carried out in the melt or in the presence of a high-boiling solvent (such as, for example, glycol, dimethylformamide, diphenylether or dichlorobenzene) conveniently at temperatures of between 25 and 200°C, but preferably at temperatures of between 70 and 150°C.

c) For the preparation of compounds of general formula I wherein at least one of the groups R_1, R_2, R_3 or R_4 represents a hydrogen atom:

cleavage of a protecting group from a compound of general formula VI



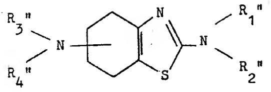
(VI)

[wherein at least one of the groups R_1', R_2', R_3' or R_4' represent a protecting group for an amino group such as, for example, an acyl or alkoxycarbonyl group (e.g. an acetyl, propionyl, methoxycarbonyl or ethoxycarbonyl group) or R_1' and R_2' or R_3' and R_4' together with the nitrogen atom between them represent an imido group (e.g. a phthalimido group); and the remaining groups R'_1, R'_2, R'_3 and R'_4 have, other than the acyl groups, the meanings given for R_1 to R_4 hereinbefore].

The cleavage of a protecting group is preferably carried out by hydrolysis in the presence of a base such as, for example, sodium hydroxide solution or potassium hydroxide solution or in the presence of an acid such as, for example, hydrochloric acid or sulphuric acid, in the presence of an aqueous solvent (such as, for example, water/ethanol, water/dioxan or water/tetrahydrofuran) at temperatures of between 50 and 150°C, but preferably at the boiling temperature of the reaction mixture. An imido group, such as the phthalimido group used as a protecting group, is preferably split off with hydrazine in the presence of a solvent such as, for example, water, water/ethanol or water/dioxan at the boiling temperature of the solvent used.

d) For the preparation of compounds of general formula I as hereinbefore defined wherein at least one of the groups R_1, R_2, R_3 or R_4 represents an alkyl or phenylalkyl group:

Reduction of a compound of general formula VII



(VII)

(wherein

at least one of the groups $R_1"$, $R_2"$, $R_3"$ or $R_4"$ represents one of the acyl or phenylacyl groups mentioned hereinbefore; and

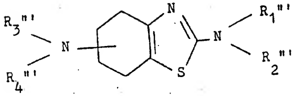
the remaining groups $R"_1$, $R"_2$, $R"_3$ and $R"_4$ have the meanings given respectively for R_1, R_2, R_3 and R_4 hereinbefore) with a metal hydride.

The reduction is conveniently carried out in a suitable solvent (such as, for example, diethylether, tetrahydrofuran, glycoldimethylether or dioxan) with a metal hydride, (e.g. with a complex metal hydride such as, for example, lithium aluminium hydride) at temperatures of between 0 and 100°C, but preferably at temperatures of between 20 and 80°C.

For the preparation of compounds of general formula I wherein the group R_3 represents one of the acyl groups mentioned hereinbefore, it is particularly advantageous to carry out the reaction with lithium aluminium hydride at temperatures of between 0 and 30°C, but preferably at ambient temperature.

e) For the preparation of compounds of general formula I as hereinbefore defined wherein at least one of the groups R_1, R_2, R_3 or R_4 represents an alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl groups:

Reaction of a compound of general formula VIII



(VIII)

(wherein the groups R_1''', R_2''', R_3''' and R_4''' are as defined above for R_1, R_2, R_3 and R_4 respectively with the proviso that at least one of R_1''', R_2''', R_3''' and R_4''' represents a hydrogen atom) with a compound of general formula IX

$$R_5 - Z \qquad \text{(IX)}$$

[wherein R_5 represents an appropriate alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group; and Z represents a nucleophilic leaving group (such as, for example, a halogen atom or a sulphonic acid group, e.g. a chlorine, bromine or iodine atom or a methoxysulphonyloxy or p-toluenesulphonyloxy group); or Z together with an adjacent hydrogen of the group R_5 represents an oxygen atom].

The reaction is conveniently carried out in the presence of a solvent (such as, for example water, methanol, ethanol, tetrahydrofuran, dioxan, acetone, acetonitrile or dimethylsulphoxide) with an alkylating agent (such as, for example, methyl iodide, dimethyl sulphate, ethyl bromide, diethyl sulphate, allyl iodide, benzyl bromide, 2-phenylethyl bromide or methyl-p-toluene sulphonate), optionally in the presence of a base (such as, for example,

sodium hydroxide solution, potassium carbonate, sodium hydride, potassium-tert.butoxide or triethylamine) conveniently at temperatures of between -10 and 50°C, but preferably at temperatures of between 0 and 30°C. However, the reaction may also be carried out in the absence of a solvent.

Alkylation of the nitrogen atom may also be effected using formaldehyde/formic acid at elevated temperatures (e.g. at the boiling temperature of the reaction mixture) or with a corresponding carbonyl compound and a complex metal hydride (such as, for example, sodium borohydride or sodium cyanoborohydride) in the presence of a solvent (such as, for example, water/methanol, ethanol, ethanol/water, dimethyl formamide or tetrahydrofuran) at temperatures of between 0 and 50°C, but preferably at ambient temperature.

If, according to the invention, a compound of general formula I is obtained wherein at least one of the groups R_1 and R_3 represents a hydrogen atom, this may be converted by corresponding acylation into a corresponding compound of general formula I wherein at least one of the groups R_1 and R_3 represents one of the acyl groups mentioned hereinbefore.

The subsequent acylation is conveniently carried out in the presence of a solvent (such as, for example, methylene chloride, chloroform, carbontetrachloride, ether, tetrahydrofuran, dioxan, glacial acetic acid, benzene, toluene, acetonitrile or dimethylformamide) optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionylchloride, N,N-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenyl-

phosphine/carbontetrachloride, or an agent which activates the amino group (e.g. phosphorus trichloride) and optionally in the presence of an inorganic base (such as, for example, sodium carbonate) or a tertiary organic base (such as, for example, triethylamine or pyridine, which may itself be used as solvent) at temperatures of between -25°C and 250°C, but preferably at temperature of between -10°C and the boiling temperatures of the solvent used. The reaction may also be carried out in the absence of a solvent and furthermore any water formed during the reaction may be removed by azeotropic distillation (e.g. by heating with toluene using a water separator, or by adding a drying agent such as magnesium sulphate or molecular sieve).

The compounds of general formula I which have at least one chiral centre can be resolved into their enantiomers by conventional methods e.g. by column chromatography on a chiral phase, by fractional crystallisation of the diastereomeric salts or by column chromatography of their conjugates with optically active auxiliary acids such as tartaric acid, O,O-dibenzoyl-tartaric acid, camphor acid, camphorsulphonic acid or α-methoxy-phenylacetic acid.

The compounds of general formula I obtained from the processes according to the invention may, if desired, subsequently be converted into acid addition salts thereof, particularly the physiologically acceptable acid addition salts with inorganic or organic acids, for example by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acid in a suitable solvent. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric,

lactic, citric, tartaric, succinic, maleic or fumaric acids. Conversely the acid addition salts of the compounds of general formula I obtained may, if desired, subsequently be converted into compounds of general formula I.

The compounds of general formulae II to IX used as starting materials are known from the literature in some cases or may be obtained using methods known from the literature.

Thus, for example, a compound of general formula II may be obtained by halogenation of the corresponding cyclohexanone, which may in turn be prepared by oxidation of the corresponding cyclohexanol and optional subsequent alkylation and/or acylation.

Compounds of general formulae VI, VII and VIII used as starting materials may be obtained by condensation of a corresponding α-bromo-cyclohexanone with a correponding thiourea.

The compounds according to the invention wherein at least one of the groups R_1 to R_4 represents one of the acyl groups mentioned hereinbefore may be used as intermediate products for preparing the compounds of general formula I wherein R_1 to R_4 have the meanings given to R_1 to R_4 hereinbefore, with the exception of the acyl groups referred to hereinbefore. These compounds display an effect on blood pressure, a heart rate-lowering effect and an effect on the central nervous system, particularly a stimulant effect on the dopamine receptors.

For example, the following compounds have been tested with regard to their effect on presynaptic dopamine receptors:

A = 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride;

B = 2-amino-6-pyrrolidino-4,5,6,7-tetrahydro-

benzthiazol-dihydrochloride;

C = 2-amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride;

D = 2-allylamino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride;

E = 6-[N-allyl-N-(4-chloro-benzyl)-amino]-2-amino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride; and

F = 2-amino-6-diallylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride.

Initially the effect on the exploratory activity of mice was tested and then, after any effect on postsynaptic dopamine receptors had been clarified (motility in animals pretreated with reserpine), the effect on dopamine turnover and dopamine synthesis was determined.

1. <u>Inhibition of the exploratory activity of mice</u>

The exploratory activity of mice in observation cages each fitted with an infra-red light barrier was recorded as the frequency of interruption of the light beam by a group of 5 mice within 5 minutes. Groups of 5 animals were given the test substance by subcutaneous injection, in a dosage of 10 mg/kg, unless otherwise specified. One hour later the animals were moved into the observation cages where their exploratory activity over a period of 5 minutes was immediately measured. In parallel or alternately with groups treated with test substance, control groups treated with common salt were investigated

(0.9% solution; 0.1 ml/10 g of body weight by subcutaneous route).

The results are displayed in the following table:

Substance	Dosage (mg/kg s.c.)	Inhibition of activity compared with controls treated with common salt (in percent)
A	2.7[1]	50
B	10.0	94
C	10.0	20[2]
D	10.0	76[2]
E	10.0	56[2]
F	10.0	60[2]

1) read off from the dosage/activity curve in the range from 1-10 mg/kg subcutaneously

2) measurement of exploration: 75 minutes after administration of the substance

2. <u>Determination of the inhibition of dopamine turnover</u>

The inhibition of dopamine turnover was measured in mice. In animals treated with α-methylparatyrosine (AMPT) (250 mg/kg by intraperitoneal route) 15 minutes into the experiment, the dopamine concentration throughout the brain decreases as the test progresses. By the administration of substances which act on autoreceptors, the dopamine reduction (compared with control animals treated with common salt solution) can be inhibited.

Test substances were administered at time

0 of the experiment in a dosage of 5 mg/kg s.c., unless otherwise stated. Four hours and 15 minutes into the experiment the animals were killed and the dopamine in the brains was determined using high pressure liquid chromatography with electrochemical detection. This allowed the percentage inhibition of the dopamine reduction induced by AMPT, caused by the test substance, to be calculated.

Substance	Dosage (mg/kg s.c.)	% inhibition of AMPT effect
A	0.95[1]	50
B	5	67
D	5	52
E	5	32

1) read off from the dosage/activity curve in the range from 0.5-3 mg/kg s.c.

3. <u>Determination of the inhibition of dopamine synthesis</u>

For this purpose, 5 animals were given the test substance in a dosage of 10 mg/kg s.c., unless otherwise stated. After 5 minutes, 750 mg/kg of γ-butyrolactone were administered, by intraperitoneal route, to rule out the effect of postsynaptic feedback loops on the rate of dopamine synthesis by blocking the presynaptic impulse line. This results in a considerable increase in the synthesis of DOPA or dopamine. In order to inhibit the decarboxylation of DOPA, 200 mg/kg of 3-hydroxybenzyl-hydrazine-hydrochloride were administered by intraperitoneal

route after a further 5 minutes. Forty minutes after administration of the test substance the animals were killed and the corpus striatum was prepared. The DOPA content was measured by HPLC with electrochemical detection (standard: dihydroxybenzylamine).

The percentage inhibition of DOPA accumulation stimulated by γ-butyrolactone, produced by the test substance compared with the control animals treated with 0.9% common salt solution was determined.

The results of these experiments are shown in the following table:

Substance	Dosage (mg/kg s.c.)	Inhibition of DOPA accumulation compared with controls treated with common salt (in percent)
A	0.55[1]	50
C	10	60

1) read off from the dosage/activity curve in the range from 0.1-1.0 mg/kg subcutaneously.

4. <u>Determination of the anti-Parkinsonism activity (the activity against Parkinson's disease)</u>

The discovery of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston <u>et al.</u>, Science <u>219</u>, 979 (1983)) provided an animal model for Parkinson's disease.

The irreversible neurological syndrome triggered by MPTP in man and in monkeys largely resembles

the idiopathic Parkinson's disease in its clinical, pathological, biochemical and pharmacological characteristics (Markey et al., Nature 311, 464 (1984)). The reason for this convincing similarity is that MPTP selectively destroys the small group of dopaminergic nerve cells in the substantia nigra of the brain which are also destroyed by degenerative processes in naturally occurring Parkinson's disease. It may be that idiopathic Parkinson's disease is caused by the formation of MPTP or a similar compound in the organism (Snyder, S.H., Nature 311, 514 (1984)). The clinical impression of the MPTP-Parkinson picture has hitherto only been demonstrated in monkeys and man, possibly as a result of its specific metabolism.

The MPTP model in Rhesus monkeys is therefore exceptionally suitable for testing the activity of anti-Parkinson's disease drugs. Seven Rhesus monkeys were given MPTP (for 3 days, 1 x 0.15 mg/kg i.m. daily, 3 days break, then 3 days 1 x 0.30-0.40 mg/kg daily) and showed the following symptoms: the animals were akinetic and not capable of taking water or food; they showed a typical bowed posture; occasional cataleptic states occured; the extremities showed rigor which was interrupted by clonic convulsions on passive movement; voluntary movements of the rump and the extremities could not usually be triggered even by very powerful and painful stimulation.

After intramuscular administration of compound C (10-100 ug/kg) voluntary movements first occured after a time interval of 5 to 10 minutes, which were followed in the subsequent 10 to 30 minutes by a gradual but extensive normalisation of the motor function. The animals were capable of taking food. They stayed perfectly upright and straight inside their cages and were also satisfactory in terms of their vigilance and species-specific behaviour.

The only residual symptoms recorded were an occasional transient and slight resting tremor and a reduction in rough strength. There was no sedation. Circulation in the skin appeared to be greater than before the compound C was administered.

The effect of compound C diminished after about 5 to 7 hours and the animals reverted to the Parkinson symptoms described above; a fresh administration of this compound again led to an improvement or substantial removal of the clinically pathological manifestations. The advantageous effects of the compounds were thus reproduced several times in each individual animal.

No side effects were detected at the dosages used hitherto.

Moreover, the compounds prepared according to the invention are largely non-toxic. Thus, when the substances were tested in mice at dosages of between 27 and 50 mg/kg s.c., no deaths were recorded.

In view of their pharmacological properties, the compounds of general formula I prepared according to the invention and the physiologically acceptable acid addition salts thereof are suitable for the treatment of central nervous, neuropsychiatric diseases, particularly schizophrenia, for the treatment of Parkinsonism or Parkinson's disease and/or for treating circulatory disorders, particularly hypertension.

According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of general formula I as hereinbefore defined or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutical carriers and/or excipients.

For pharmaceutical administration the active ingredient may be incorporated into preparations

in either liquid or solid form using carriers and excipients conventionally used in the pharmaceutical art, optionally in combination with other active ingredients. Preferred forms include, for example, plain or coated tablets, powders, suppositories, suspensions, drops or ampoules.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units contain from 0.01 to 0.5 mg/kg of body weight, preferably from 0.1 to 0.3 mg/kg of body weight, and the daily dose may, for example, consist of 1 to 4 dosage units. The total daily dose may, however, be varied according to the compound used, the subject treated and the complaint concerned.

The following non-limiting examples are intended to illustrate the invention in more detail:

Example A

4-[N-(4-Chloro-benzyl)-amino]-cyclohexanol

75.8 g (0.5 Mol) of 4-amino-cyclohexanol-hydrochloride are dissolved in 60 ml of water and, after the addition of 36 g (0.26 Mol) of potassium carbonate and 500 ml of toluene, boiled with a water separator until the separation of water is complete. Then 71.7 g (0.5 Mol) of 4-chlorobenzaldehyde are slowly added with further boiling using the water separator. After the calculated quantity of water has been separated, the residue is added to water and the toluene phase is separated off and concentrated. The concentration residue is dissolved in 500 ml of ethanol and 19 g (0.5 Mol) of sodium borohydride are added in batches with stirring. After standing overnight, the mixture is concentrated, mixed with water and extracted with chloroform. After drying and concentrating the extracts, the residue is recrystallised from ethyl acetate.

Yield: 93.4 g (78% of theory),

M.p.: 103-104°C

Calculated:	C 65.12	H 7.57	N 5.84	Cl 14.79
Found:	65.21	7.68	5.93	14.65

The following compound was prepared analogously to Example A using propionaldehyde:

4-n-propylamino-cyclohexanol

Yield: 12.4% of theory,

M.p.: $<$ 20°C

Calculated: m/e = 157

Found: m/e = 157

Example B

4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanol

7.2 g (30 mMol) of 4-[N-(4-chloro-benzyl)-amino]-cyclohexanol are dissolved in 30 ml of dimethylformamide, and after the addition of 2.2 g (16 mMol)

of potassium carbonate, 4.26 g (30 mMol) of methyliodide are added dropwise. When the slightly exothermic reaction is complete, the mixture is concentrated by evaporation, mixed with water and extracted with chloroform. The concentrated extracts are chromatographed on silica gel to purify them (eluant: methylene chloride/methanol = 20/1).

Yield: 3.3 g (43.4% of theory),

M.p.: 74-75°C

	C	H	N	Cl
Calculated:	66.26	7.94	5.52	13.97
Found:	66.36	7.95	5.46	13.81

The following compounds were prepared analogously to Example B:

4-Hexamethyleneimino-cyclohexanol

Prepared from 4-amino-cyclohexanol and 1,6-dibromohexane.

Yield: 47.3% of theory,

M.p.: < 20°C

Calculated: m/e = 197

Found: m/e = 197.

4-Diallylamino-cyclohexanol

Prepared from 4-amino-cyclohexanol and allylbromide.

Yield: 51% of theory,

M.p.: < 20°C

Calculated: m/e = 195

Found: m/e = 195.

4-Piperidino-cyclohexanol

Prepared from 4-amino-cyclohexanol and 1,5-dibromopentane.

Yield: 65.8% of theory,

M.p.: < 20°C

Calculated: m/e = 183
Found: m/e = 183.

4-Pyrrolidino-cyclohexanol

Prepared from 4-amino-cyclohexanol and 1,4-dibromo-butane.
Yield: 35.8% of theory,
M.p.: $<$ 20°C
Calculated: m/e = 169
Found: m/e = 169.

Example C

4-Diethylamino-cyclohexanol

28.75 g (0.25 Mol) of 4-amino-cyclohexanol are dissolved in 150 ml of water, with the addition of 20 g (0.5 Mol) of sodium hydroxide and then 65.6 ml (0.5 Mol) of diethylsulphate are added dropwise. The mixture then heats up to 65°C. It is stirred at 70°C for one hour and then poured onto ice and extracted with chloroform.
Yield: 18.2 g (42.5% of theory),
M.p.: $<$ 20°C
Calculated: m/e = 171
Found: m/e = 171.

Example D

4-[N-(4-Chloro-benzyl)-amino]-cyclohexanone

23.9 g (0.1 Mol) of 4-[N-(4-chlorobenzyl)-amino]-cyclohexanol are suspended in 125 ml of ice water and then 32 ml of concentrated sulphuric acid are added. Then 29.4 g (0.1 Mol) of potassium dichromate are added in 2 batches and the mixture is heated for 5 hours at 50°C. It is then cooled, made alkaline with sodium hydroxide solution and

then extracted with chloroform. After concentration, a yellowish oily liquid is obtained.

Yield: 8.2 g (34% of theory),
M.p.: < 20°C
Calculated: m/e = 237/239
Found: m/e = 237/239.

The following compounds were prepared analogously to Example D:

4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanone

Yield: 38% of theory,
M.p.: < 20°C
Calculated: m/e = 251/253
Found: m/e = 251/253.

4-Diallylamino-cyclohexanone

Yield: 21% of theory,
M.p.: < 20°C
Calculated: m/e = 193
Found: m/e = 193.

4-Piperidino-cyclohexanone

Yield: 22.2% of theory,
M.p.: < 20°C
Calculated: m/e = 181
Found: m/e = 181.

4-Pyrrolidino-cyclohexanone

Yield: 45.1% of theory,
M.p.: < 20°C
Calculated: m/e = 167
Found: m/e = 167.

4-Diethylamino-cyclohexanone

Yield: 49.7% of theory,
M.p.: < 20°C
Calculated: m/e = 169
Found: m/e = 169.

4-n-Propylamino-cyclohexanone

Yield: 33% of theory,
M.p.: < 20°C
Calculated: m/e = 155
Found: m/e = 155.

Example E
4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanone

8.4 g (35 mMol) of 4-[N-(4-chloro-benzyl)-amino]-cyclohexanone are dissolved in 50 ml of absolute dimethylformamide and, after the addition of 2.6 g (18.7 mMol) of potassium carbonate, 5.0 g (35 mMol) of methyliodide are added dropwise at 25-30°C. After standing overnight the mixture is concentrated, mixed with water and extracted with chloroform. The extracts are dried and concentrated.
Yield: 8.1 g (93% of theory),
M.p.: < 20°C
Calculated: m/e = 251/253
Found: m/e = 251/253.

The following compounds were prepared analogously to Example E:

4-[N-Allyl-N-(4-chloro-benzyl)-amino]-cyclohexanone

Yield: 70.7% of theory,
M.p.: < 20°C

Calculated: m/e = 277/279
Found: m/e = 277/279.

4-[N-(4-Chloro-benzyl)-ethylamino]-cyclohexanone

Yield: 30% of theory,
M.p.: < 20°C
Calculated: m/e = 265/267
Found: m/e = 265/267.

Example F

4-Hexamethyleneimino-cyclohexanone

A solution of 47 g (0.5 Mol) of 4-hexamethyleneimino-cyclohexanol in 300 ml of methylenechloride is added dropwise to a suspension of 107.5 g (0.5 Mol) of pyridinium chlorochromate and 40 g (0.5 Mol) of sodium acetate in 700 ml of methylenechloride at 20 to 25°C. After stirring for one hour at 20°C, the mixture is poured onto ice water and sodium hydroxide solution, and then extracted with methylene chloride. After drying and concentration of the extracts a coloured oily liquid is left.
Yield: 16.8 g (35.8% of theory),
M.p.: < 20°C
Calculated: m/e = 195
Found: m/e = 195.

Example 1

2-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

2.82 g (0.02 Mol) of 4-dimethylamino-cyclohexanone are dissolved in 20 ml of glacial acetic acid, mixed with 4.7 ml of 36% of hydrobromic acid in glacial acetic acid and then a solution of 1.0 ml (0.02 Mol) of bromine in 12 ml of glacial acetic acid is added dropwise with cooling. The mixture is then concentrated by evaporation *in vacuo* and the residue is triturated several times with diethylether. The ether extracts are discarded and the residue is dissolved in 50 ml of ethanol. After 3.04 g (40 mMol) of thiourea have been added the mixture is refluxed for 5 hours. It is then concentrated by evaporation, made alkaline with sodium hydroxide solution and extracted with chloroform. After drying and concentration of the extracts, the residue is purified by column chromatography on silica gel (eluant: chloroform/methanol = 1/1). Then the base (mp: 191°C) is dissolved in acetone and converted into the dihydrochloride with isopropanolic hydrochloric acid.

Yield: 1.09 g (20% of theory),

M.p.: 272°C

Calculated:	C 40.00	H 6.34	N 15.55	Cl 26.24
Found:	39.63	6.55	15.31	26.29

The following tetrahydrobenzthiazoles were prepared analogously to Example 1 from the corresponding ketones:

2-Amino-6-diethylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 25% of theory,

M.p.: 182-183°C

Calculated: C 58.62 H 8.49 N 18.64

Found: 58.65 8.72 18.50

2-Amino-6-piperidino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 13% of theory,
M.p.: 280°C
Calculated: C 46.45 H 6.82 N 13.55 Cl 22.85
Found: 46.37 6.75 13.41 22.95

2-Amino-6-pyrrolidino-4,5,6,7-tetrahydro-benzthiazole
Yield: 24.4% of theory,
M.p.: 204-206°C
Calculated: C 59.15 H 7.67 N 18.81
Found: 59.50 7.74 18.95

2-Amino-6-diallylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 19% of theory,
M.p.: 242°C
Calculated: C 48.44 H 6.56 N 13.03 Cl 22.00
Found: 47.90 6.49 12.95 22.21

2-Amino-6-[N-(4-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole
Yield: 35% of theory,
M.p.: 146°C
Calculated: C 57.23 H 5.49 N 14.30 Cl 12.06
Found: 56.93 5.56 13.86 12.04

2-Amino-6-[N-(4-chloro-benzyl)-methylamino]-4,5,6,7-tetrahydro-benzthiazole
Yield: 36% of theory,
M.p.: 163°C
Calculated: C 58.69 H 5.89 N 13.64 Cl 11.51
Found: 58.50 5.94 13.49 11.55

2-Amino-6-[N-(4-chloro-benzyl)-ethylamino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 49% of theory,
M.p.: 258°C (decomposition)

Calculated:	C 48.67	H 5.61	N 10.64	Cl 26.94
Found:	48.30	5.85	10.57	26.97

2-Amino-6-[N-allyl-N-(4-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 46.5% of theory,
M.p.: 240°C (decomposition)

Calculated:	C 50.19	H 5.45	N 10.33	Cl 26.14
Found:	49.84	5.68	9.97	26.04

2-Amino-6-hexamethyleneimino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 15.4% of theory,
M.p.: 295°C (decomposition)

Calculated:	C 48.17	H 7.14	N 12.95	Cl 21.86
Found:	47.90	7.34	12.44	21.64

2-Allylamino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 4-dimethylamino-cyclohexanone by bromination and subsequent reaction with allylthiourea.
Yield: 64% of theory,
M.p.: 248°C

Calculated:	C 46.45	H 6.82	N 13.54	Cl 22.85
Found:	46.30	7.00	13.29	22.99

2-Amino-5-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 3-dimethylamino-cyclohexanone.
Yield: 33% of theory,
M.p.: 194°C

Calculated:	C 40.00	H 6.34	N 15.55	Cl 26.24
Found:	39.74	6.37	15.15	25.96

2-Amino-5-morpholino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 3-morpholino-cyclohexanone.

Yield: 7.4 g (20% of theory),
M.p.: 237-238°C

Calculated:	C 42.31	H 6.13	N 13.46
Found:	42.00	6.29	13.13

Example 2

2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

a) (4-(Phthalimido)-cyclohexanol

75.5 g (0.5 Mol) of 4-aminocyclohexanol-hydrochloride and 74.0 g (0.5 Mol) of phthalic acid anhydride are mixed with 65 g (0.5 Mol) of ethyl-diisopropyl-amine and 1000 ml of toluene and boiled for 36 hours with a water separator. Water is then added, the toluene phase is separated off and the aqueous phase is extracted several times with chloroform. The organic phases are combined, dried and concentrated. The concentration residue is recrystallised from isopropanol.
Yield: 95 g (77.8% of theory),
M.p.: 175-176°C.

b) 4-(Phthalimido)-cyclohexanone

95 g (0.388 Mol) of 4-(phthalimido)-cyclohexanol are dissolved in 600 ml of chloroform and, after the addition of 450 ml of water and 120 ml of sulphuric acid, 90 g (0.3 Mol) of potassium dichromate are added in batches. The internal temperature of the mixture is maintained at between 25 and 30°C by slight cooling. The mixture is stirred for a further 3 hours and then the chloroform phase is separated off and the mixture extracted twice more with chloroform. After drying and concentration of the extracts

82 g (86.9% of theory) are obtained.

c) 2-Amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole

48.6 g (0.2 Mol) of 4-(phthalimido)-cyclohexanone are brominated analogously to Example 1 with 32 g (0.2 Mol) of bromine and then converted with thiourea into the 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole.

Yield: 30 g (50% of theory),

M.p.: 244-246°C (decomposition)

Calculated:	C 60.18	H 4.38	N 14.04
Found:	60.05	4.25	13.95

d) 2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

9.5 g (31.7 mMol) of 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole are suspended in 100 ml of ethanol and, after the addition of 1.8 g (36 mMol) of hydrazine hydrate, refluxed for 2 hours. The mixture is then concentrated and purified by column chromatography on silica gel using methanol as eluant. The dihydrochloride is precipitated with ethanolic hydrochloric acid.

Yield: 2.0 g (26% of theory),

M.p.: > 315°C (decomposition)

Calculated:	C 34.72	H 5.41	N 17.35	Cl 29.25
Found:	35.00	5.26	16.95	29.10

Example 3

6-Acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide

160 g (1.0 Mol) of bromine are added dropwise to a solution of 155 g (1.0 Mol) of 4-acetylamino-

cyclohexanone in 1.5 l of glacial acetic acid. The mixture is stirred for 3 hours at ambient temperature. 152.0 g (2.0 Mol) of thiourea are added to the reaction mixture and the resulting mixture is refluxed for 30 minutes. After cooling, the precipitated crystals are suction filtered and washed with water and acetone.

Yield: 73 g (37% of theory),

M.p.: 292-293°C (decomposition)

Calculated:	C 36.99	H 4.83	N 14.38
Found:	36.82	4.76	14.18

By stirring the hydrobromide in aqueous potassium carbonate solution and subsequently suction filtering, the free base is obtained, m.p. 194-196°C (methanol).

The following compounds were prepared analogously to Example 3:

6-Acetylamino-2-allylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 46% of theory,

M.p.: 194-196°C

Calculated: m/e = 251

Found: m/e = 251

6-Acetylamino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 64% of theory,

M.p.: 238-240°C

Calculated:	C 53.30	H 6.71	N 18.65
Found:	53.18	6.78	18.41

6-Acetylamino-2-dimethylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 51% of theory,

M.p.: 170-171°C

Calculated:	C 55.20	H 7.16	N 17.56
Found:	55.15	7.17	17.58

Example 4

2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide

3 g (0.01 Mol) of 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide are dissolved in 20 ml of semi-concentrated hydrobromic acid and refluxed for 6 hours. The solution is then concentrated by evaporation and the residue recrystallised from methanol.

Yield: 2.8 g (82% of theory),
M.p.: >315°C,
Melting point of the base: 233-236°C

Calculated:	C 25.39	H 3.96	N 12.69
Found:	25.34	3.93	12.51

The following compounds were prepared analogously to Example 4:

6-Amino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide
Yield: 57% of theory,
M.p.: 262-263°C

Calculated:	C 36.37	H 5.34	N 15.90
Found:	36.30	5.45	15.82

2-Allylamino-6-amino-4,5,6,7-tetrahydro-benzthiazole-oxalate
Yield: 52% of theory,
M.p.: 164-165°C (decomp.)
Calculated: m/e = 209
Found: m/e = 209

6-Amino-2-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide
Yield: 45% of theory,
M.p.: >270°C (decomp.)
Calculated: C 30.10 H 4.77 N 11.70

Found:	30.13	4.84	11.68

Example 5

2-Amino-6-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

5 g (0.022 Mol) of 2-phenyl-ethylbromide and 2.6 g of potassium carbonate are added to a solution of 3.4 g (0.02 Mol) of 2,6-diamino-tetrahydro-benzthiazole in 34 ml of dimethylformamide and the reaction mixture is stirred at 100°C for 3 hours. The potassium bromide precipitate is then suctioned off and the solvent is distilled off. The residue is chromatographed on silica gel (ethyl acetate/methanol = 80/20 + 3% ammonia). The desired compound crystallises out from ethereal hydrochloric acid.

Yield: 2.1 g (30% of theory),

M.p.: 289-291°C

Calculated:	C 52.02	H 6.11	N 12.13
Found:	51.82	6.13	12.16

The following compounds were prepared analogously to Example 5:

2-Amino-6-isopropylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 28% of theory,

M.p.: 295-296°C (decomp.)

Calculated:	C 42.25	H 6.74	N 14.78
Found:	41.95	7.09	14.50

2-Amino-6-isobutylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 35% of theory,

M.p.: 268°C (decomp.)

Calculated:	C 44.29	H 7.10	N 14.09
Found:	43.97	7.17	13.97

6-Allylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 38% of theory,
M.p.: 282-283°C (decomp.)

Calculated:	C 42.56	H 6.07	N 14.89
Found:	42.17	6.07	14.71

2-Amino-6-[N-(2-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 40% of theory,
M.p.: > 280°C (decomp.)

Calculated:	C 45.85	H 4.95	N 11.45
Found:	45.50	4.86	11.08

2-Amino-6-propargylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 35% of theory,
M.p.: 268-270°C (decomp.)

Calculated:	C 42.86	H 5.40	N 15.00
Found:	42.78	5.59	14.79

2-Amino-6-methylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide
Yield: 25% of theory,
M.p.: 312-313°C (decomp.)

Calculated:	C 27.84	H 4.38	N 12.18
Found:	27.78	4.46	12.21

Example 6

2-Amino-6-di-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride-monohydrate

To a solution of 3.4 g (0.02 Mol) of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole in 50 ml of methanol are added 10 g (0.08 Mol) of n-propylbromide and 11.1 g of potassium carbonate and the mixture is refluxed for 3 days. 100 ml of water are

added and the mixture is extracted with ethylacetate. The solvent is distilled off and the residue is chromatographed on silica gel (eluant: methylenechloride/methanol = 80/20). The corresponding fraction is concentrated by evaporation and the desired compound is precipitated in the form of the hydrochloride.

Yield: 1.9 g (28% of theory),

M.p.: 271-273°C

	C	H	N
Calculated:	45.34	7.90	12.20
Found:	45.00	7.98	12.00

Example 7

2-Amino-6-n-butylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

To a solution of 3.4 g (0.02 Mol) of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole in 34 ml of dimethylformamide are added 1.8 g (0.022 Mol) of n-butanal and the mixture is heated to 50°C for 1 hour. After cooling, the reaction solution is mixed with 0.8 g (0.02 Mol) of sodium borohydride and heated to 50°C for 30 minutes. The solvent is largely eliminated *in vacuo*. Whilst cooling with ice, the residue is mixed with 20 ml of water and 2N hydrochloric acid until a pH of 1 is obtained. The aqueous solution is extracted with ethylacetate and the organic phase discarded. The aqueous phase is mixed with potassium carbonate until an alkaline reaction is obtained and then extracted with ethyl acetate. The organic phase is dried and concentrated. The compound crystallizes out when ethereal hydrochloric acid is added.

Yield: 2.3 g (39% of theory),

M.p.: 254-256°C

	C	H	N
Calculated:	44.29	7.10	14.09
Found:	44.44	7.31	14.07

The following compounds were prepared analogously to Example 7:

2-Amino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 38% of theory,
M.p.: 296-297°C

Calculated:	C 40.00	H 6.34	N 15.55
Found:	39.97	6.41	15.35

2-Amino-6-n-pentylamino-4,5,6,7-tetrahydro-benzthiazole-semifumarate
Yield: 42% of theory,
M.p.: >270°C

Calculated:	C 56.54	H 7.79	N 14.13
Found:	56.13	7.80	13.97

2-Amino-6-n-hexylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 49% of theory,
M.p.: 272-274°C

Calculated:	C 47.85	H 7.72	N 12.88
Found:	47.96	7.65	12.71

2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 42% of theory,
M.p.: 286-288°C

Calculated:	C 42.25	H 6.74	N 14.78
Found:	42.05	6.77	14.57

(-) 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole dihydrochloride
M.p.: 270-272°C
$\alpha_D^{20} = -56°$ (c = 1, methanol)

(+) 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole dihydrochloride
M.p.: 270-272°C
α_D^{20} = +56° (c = 1, methanol)

2-Amino-6-cyclopentylamino-4,5,6,7-tetrahydro-benzthiazole-dioxalate
Yield: 36% of theory,
M.p.: 212-213°C

Calculated:	C 46.04	H 5.55	N 10.07
Found:	45.95	5.28	10.08

2-Amino-6-cyclohexylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 38% of theory,
M.p.: 288-290°C

Calculated:	C 48.14	H 7.15	N 12.96
Found:	47.88	7.16	12.74

<u>Example 8</u>

<u>6-Ethylamino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride</u>

A solution of 1 g (4.4 mMol) of 6-acetylamino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole in 20 ml of absolute tetrahydrofuran is mixed with 0.4 g (0.01 Mol) of lithium aluminium hydride and refluxed for 2 hours. After cooling, 50 g of a 40% diammonium tartrate solution are added dropwise. The organic phase is separated off and concentrated by evaporation. The residue is chromatographed on silica gel (eluant: methylene chloride/methanol = 80/20). The corresponding fraction is concentrated by evaporation. The compound crystallizes out when ethereal hydrochloric acid is added.
Yield: 0.3 g (33% of theory),
M.p.: > 260°C
Calculated: m/e = 211

Found: m/e = 211

The following compounds were prepared analogously to Example 8:

2-Allylamino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
Yield: 37% of theory,
M.p.: 218-220°C (decomp.)

Calculated:	C 46.45	H 6.82	N 13.54
Found:	46.60	7.03	13.66

2-Dimethylamino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-oxalate hydrate
Yield: 20% of theory,
M.p.: 189-190°C

Calculated:	C 46.83	H 6.95	N 12.60
Found:	47.03	6.89	12.49

Example 9

6-Acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-benzthiazole

To a solution of 4.2 g (0.02 Mol) of 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole in 100 ml of absolute tetrahydrofuran are added 2.2 g (0.022 Mol) of triethylamine and 3.1 g (0.022 Mol) of benzoylchloride and the mixture is refluxed for 3 hours. The reaction mixture is mixed with water and extracted with ethyl acetate. The organic phase is concentrated by evaporation. The residue is recrystallized from methanol.

Yield: 3 g (48% of theory),
M.p.: > 260°C
Calculated: m/e = 315
Found: m/e = 315

The following compounds were prepared analogously to Example 9:

2,6-Diacetylamino-4,5,6,7-tetrahydro-benzthiazole
Yield: 50% of theory,
M.p.: 258-259°C
Calculated: m/e = 252
Found: m/e = 252

6-Acetylamino-2-propionylamino-4,5,6,7-tetrahydro-benzthiazole
Yield: 44% of theory,
M.p.: > 260°C
Calculated: m/e = 266
Found: m/e = 266

6-Acetylamino-2-phenylacetylamino-4,5,6,7-tetrahydro-benzthiazole
Yield: 78% of theory,
M.p.: 112°C
Calculated: m/e = 329
Found: m/e = 329

Example 10

2-Benzylamino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

To a solution of 1.2 g (3.2 mMol) of 6-acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-benzthiazole in 50 ml of absolute tetrahydrofuran are added 0.24 g (64 mMol) of lithium aluminium hydride and the mixture is refluxed for 1 hour. It is then worked up as in Example 8.

Yield: 0.4 g (34% of theory),
M.p.: 242-245°C

Calculated:	C 53.33	H 6.43	N 19.68
Found:	53.59	6.37	19.42

The following compounds were prepared analogously to Example 10:

2,6-Diethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 38% of theory,

M.p.: 241-243°C

Calculated:	C 44.29	H 7.10	N 14.09
Found:	44.06	7.27	13.85

6-Ethylamino-2-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 32% of theory,

M.p.: 267-268°C

Calculated:	C 46.15	H 7.42	N 13.46
Found:	45.95	7.53	13.33

6-Ethylamino-2-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride-hemihydrate

Yield: 26% of theory,

M.p.: 248-251°C

Calculated:	C 53.25	H 6.84	N 10.96
Found:	53.31	6.64	10.89

2-(4-Chloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 65% of theory,

M.p.: > 260°C

Calculated:	C 48.67	H 5.62	N 10.64
Found:	48.79	5.80	10.60

2-(2-Chloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 36% of theory,

M.p.: 251-253°C

Calculated:	C 48.67	H 5.62	N 10.64
Found:	48.57	5.78	10.57

2-(3,4-Dichloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 62.5% of theory,

M.p.: > 260°C

Calculated:	C 44.77	H 4.93	N 9.79
Found:	44.85	4.82	9.96

6-Acetylamino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 2,6-diacetylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

Yield: 33% of theory,

M.p.: 234-235°C

Calculated: m/e = 238

Found: m/e = 238

6-Acetylamino-2-benzylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 6-acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

6-Acetylamino-2-n-propylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 6-acetylamino-2-propionylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

6-Acetylamino-2-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-benzthiazole.

Example 11

6-Amino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 6-acetylamino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole analogously to Example 4.

Yield: 45% of theory,

M.p.: 155-158°C

Calculated:	C 40.00	H 6.34	N 15.55
Found:	39.86	6.31	15.26

The following compounds were prepared analogously to Example 11:

6-Amino-2-benzylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide

6-Amino-2-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide

6-Amino-2-[N-(2-phenyl-ethyl)amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide.

Example 12

2-Benzoylamino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

3.0 g. (15 mMol) of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole are dissolved in 15 ml of pyridine and 2.1 g (15 mMol) of benzoylchloride are added dropwise. After standing overnight the mixture is concentrated, mixed with soda solution and extracted with chloroform. The chloroform extract is concentrated and then chromatographed on silica gel (eluant: methylenechloride/methanol = 9/1). The isolated base (melting point 174°C) is dissolved in acetone and the dihydrochloride is precipitated with isopropanolic hydrochloric acid.

Yield: 2.8 g (49% of theory),

M.p.: 284°C (decomp.)

Calculated:	C 51.33	H 5.65	N 11.23	Cl 18.94
Found:	51.51	5.76	11.32	18.75

Example 13

6-Acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole

3.1 g (20 mMol) of 4-acetylamino-cyclohexanone and 6.2 g (20 mMol) of formamidine-disulphide-dihydrobromide are intimately mixed and heated at a temperature of 120 - 130°C for 2 hours with stirring. The mixture is then taken up in water, made alkaline with ammonia and extracted with chloroform. After the extracts have been dried they are concentrated by evaporation, triturated with acetone and suction filtered.

Yield: 1.8 g (42.6% of theory),
M.p.: 195°C

Calculated:	C 51.17	H 6.20	N 19.89
Found:	51.09	6.22	19.75

Starting from 4-dimethylamino-cyclohexanone the following compound was prepared analogously to Example 13:

2-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole
Yield: 21% of theory,
M.p.: 189-190°C

Calculated:	C 54.80	H 7.66	N 21.29
Found:	54.71	7.53	21.12

Example I

Tablet core containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Composition:

1 tablet core contains:

Active substance	5.0 mg
Lactose	33.5 mg
Corn starch	10.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Preparation

A mixture of the active substance with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a screen with a mesh size of 1 mm, dried at 40°C and again rubbed through this screen. The granulate thus obtained is mixed with magnesium stearate and compressed to form tablet cores. The tablets must be prepared in darkened rooms.

Weight of core: 50 mg
Punch: 4 mm, convex.

The tablet cores thus obtained are coated by the usual method with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with bees wax.

Weight of coated tablet: 100 mg.

Example II

Drops containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Composition:

100 ml of drops substance:

Methylester-p-hydroxybenzoate	0.035 g
n-Propylester-p-hydroxybenzoate	0.015 g
Anisol	0.05 g
Menthol	0.06 g
Pure ethanol	10.0 g
Active substance	0.5 g
Citric acid	0.7 g
Sec. sodiumphosphate x 2 H_2O	0.3 g
Sodium cyclamate	1.0 g
Glycerol	15.0 g
Distilled water	ad 100.0 ml

Preparation

The p-hydroxybenzoates, anisol and menthol are dissolved in ethanol (Solution I).

The buffer substances, active substance and sodium cyclamate are dissolved in distilled water and glycerol is added (Solution II). Solution I is stirred into Solution II and the mixture is topped up to the volume specified with distilled water. The finished drops solution is filtered through a suitable filter. The preparation and bottling of the drops solution must be carried out away from the light and under a protective gas.

Example III

Suppositories containing 10 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

1 suppository contains:	
Active substance	10.0 mg
Suppository mass (e.g. Witepsol W 45)	1 690.0 mg
	1 700.0 mg

Preparation

The finely powdered substance is stirred into the molten suppository mass, cooled to 40°C, with an immersion homogeniser. At 35°C the mass is poured into slightly chilled moulds.
Weight of suppository: 1.7 g

Example IV

Ampoules containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

1 Ampoule contains:		
Active substance		5.0 mg
Citric acid		7.0 mg
Sec. sodium phosphate x $2H_2O$		3.0 mg
Sodium pyrosulphite		1.0 mg
Distilled water	ad.	1.0 ml

Preparation

The buffer substances, active substance and sodium pyrosulphite are successively dissolved in deionised water which has been cooled under CO_2 gas. The solution is made up to the volume specified with boiled water and filtered free from pyrogens.

Bottling: in brown ampoules under protective gas
Sterilisation: 20 minutes at 120°C.

The preparation and transferring of the ampoule solution must be carried out in darkened rooms.

Example V

Coated tablets containing 1 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

1 tablet core contains:

Active substance	1.0 mg
Lactose	35.5 mg
Corn starch	12.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Preparation

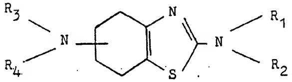
Analogous to Example I

Weight of core:	50 mg
Punch:	5 mm, convex
Weight of coated tablet:	100 mg

Obviously, instead of the compound mentioned, all the other compounds of general formula I may be incorporated as active substance in the Pharmaceutical Examples I to V, such as, for example, 2-amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride.

Claims:

1. Compounds of general formula I



(I)

[wherein

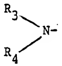
R_1 represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

R_2 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

R_3 represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms), and R_4 represents a hydrogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or R_3 and R_4 together with the nitrogen atom

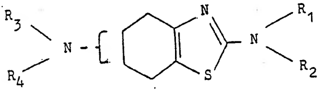
between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group] and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein the



group is in the 5 or 6-position.

3. Compounds of general formula Ia



(Ia)

(wherein

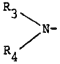
R_1 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichloro-benzyl or phenylethyl group;

R_2 represents a hydrogen atom or a methyl or ethyl group; and

R_3 represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms or an allyl, propargyl, benzyl, chlorobenzyl, phenylethyl, cyclopentyl or cyclohexyl group, and R_4 represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl group; or R_3 and R_4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group) and acid addition salts thereof.

4. Compounds as claimed in claim 3, wherein

the



group is in the 6-position.

5. Compounds as claimed in claim 3 or claim 4 (wherein

R_1 and R_2 together with the nitrogen atom between them represent an amino or allylamino group and

R_3 and R_4 together with the nitrogen atom between them represent a dimethylamino, diethylamino, N-allyl-N-(4-chloro-benzyl)-amino, n-propylamino or pyrrolidino group).

6. 2-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole, enantiomers thereof and acid addition salts thereof.

7. 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole, enantiomers thereof and acid addition salts thereof.

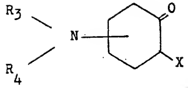
8. Physiologically acceptable acid addition salts with inorganic or organic acids of the compounds as claimed in any one of the preceding claims.

9. Salts as claimed in claim 8 formed with hydrochloric, hydrobromic, sulphuric, phosphoric, lactic, citric, tartaric, succinic, maleic or fumaric acids.

10. Compounds as claimed in claim 1 as herein specifically disclosed.

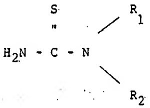
11. Compounds as claimed in claim 1 as herein specifically disclosed in any one of Examples 1 to 13.

12. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a cyclohexanone of general formula II



(II)

(wherein R_3 and R_4 are as defined in claim 1 and X represents a nucleophilic leaving group with a thiourea of general formula III



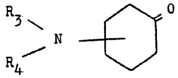
(III)

wherein R_1 and R_2 are as defined in claim 1.

13. A process as claimed in claim 12 wherein a compound of formula II in which X represents a halogen atom is used.

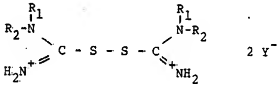
14. A process as claimed in claim 13 wherein a compound of formula II in which X represents a chlorine or bromine atom is used.

15. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a compound of general formula IV



(IV)

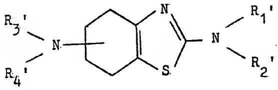
(wherein R_3 and R_4 are as defined in claim 1) with a formamidine disulphide of general formula V



(V)

(wherein R_1 and R_2 are as defined in claim 1 and Y^- represents an anion of an inorganic or organic acid).

16. A process for the preparation of compounds of general formula I wherein at least one of the groups R_1, R_2, R_3 or R_4 represents a hydrogen atom, which comprises cleaving a protecting group from a compound of general formula VI



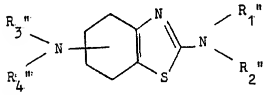
(VI)

(wherein at least one of the groups R_1', R_2', R_3' or R_4' represents a protecting group for an amino group, or R_1' and R_2' or R_3' and R_4' together with the nitrogen atom between them represent an imido group; and the remaining groups R'_1, R'_2, R'_3 and R'_4 have the meanings given for R_1 to R_4 in claim 1 other than acyl groups).

17. A process as claimed in claim 16 wherein a compound of formula V in which at least one of the groups R'_1, R'_2, R'_3 or R'_4 represents an acyl or alkoxycarbonyl group is used.

18. A process as claimed in claim 16 wherein a compound of formula V in which at least one of the groups R'_1, R'_2, R'_3 or R'_4 represents an acetyl, propionyl, methoxycarbonyl or ethoxycarbonyl group is used.

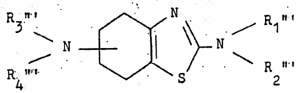
19. A process for the preparation of compounds as claimed in claim 1 wherein at least one of the groups R_1, R_2, R_3 or R_4 represents an alkyl or phenylalkyl group which comprises reducing a compound of general formula VII



VII

(wherein at least one of the groups R_1'', R_2'', R_3'' or R_4'' represents one of the acyl or phenylacyl groups mentioned hereinbefore; and the remaining groups have the meanings given respectively for R_1, R_2, R_3 and R_4 in claim 1) with a metal hydride in the presence of a solvent.

20. A process for the preparation of compounds as claimed in claim 1 wherein at least one of the groups R_1, R_2, R_3 or R_4 represents an alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group which comprises reacting a compound of general formula VIII



(VIII)

(wherein R_1''', R_2''', R_3''' and R_4''' are as defined in claim 1 for R_1, R_2, R_3 and R_4 respectively with the proviso that at least one of R_1''', R_2''', R_3''' and R_4''' represents a hydrogen atom) with a compound of general formula IX.

$$R_5 - Z \qquad \text{(IX)}$$

(wherein R_5 represents an appropriate alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group; and Z represents a nucleophilic leaving group; or Z together with an adjacent hydrogen of the group R_5 represents an oxygen atom).

21. A process as claimed in claim 20 wherein a compound of formula IX in which Z represents a halogen atom or a sulphonic acid group is used.

22. A process as claimed in claim 20 or claim 21 wherein a compound of formula IX in which Z represents a chlorine, bromine or iodine atom or a methoxysulphonyloxy or p-toluenesulphonyloxy group is used.

23. A process as claimed in any one of claims 12 to 22 wherein the reaction is carried out in

the presence of a solvent.

24. A process as claimed in any one of claims 12 to 14 wherein the reaction is carried out at temperatures of between 0 and 150°C.

25. A process as claimed in claim 24 wherein the reaction is carried out at temperatures of between 20 and 100°C.

26. A process as claimed in claim 15 wherein the reaction is carried out at temperatures of between 50 and 200°C.

27. A process as claimed in claim 26 wherein the reaction is carried out at temperatures of between 70 and 150°C.

28. A process as claimed in any one of claims 16 to 18 wherein the cleavage of a protecting group is carried out by hydrolysis in the presence of a base or acid.

29. A process as claimed in any one of claims 16 to 18 or 28 wherein the reaction is carried out at temperatures of between 50 and 150°C.

30. A process as claimed in claim 19 wherein the reduction is carried out with lithium aluminium hydride.

31. A process as claimed in claim 19 or claim 30 wherein the reduction is carried out at temperatures of between 0 and 100°C.

32. A process as claimed in claim 31 wherein the reduction is carried out at temperatures of between 20 and 80°C.

33. A process as claimed in any one of claims 20 to 23 wherein if Z represents a nucleophilic leaving group, the reaction is carried out at temperatures of between -10 and 50°C.

34. A process as claimed in claim 33 wherein the reaction is carried out at temperatures of between 0 and 30°C.

35. A process as claimed in claim 33 or claim

34 wherein the reaction is carried out in the presence of a base.

36. A process as claimed in any one of claims 20 to 23 wherein, if the reaction is carried out with a carbonyl compound of general formula IX, it is carried out in the presence of a complex metal hydride at temperatures of between 0 and 50°C.

37. A process as claimed in claim 36 wherein the reduction is carried out at ambient temperature.

38. A process as claimed in claims 36 or 37 wherein sodium borohydride or sodium cyanoborohydride is used as the complex metal hydride.

39. A process as claimed in any one of claims 12 to 38 wherein a compound of formula I thus obtained wherein at least one of the groups R_1 and R_3 represents a hydrogen atom, is converted by a suitable acylation into a corresponding compound of general formula I wherein at least one of groups R_1 and R_3 represents one of the acyl groups mentioned in claim 1.

40. A process as claimed in any one of claims 12 to 39 wherein a compound of formula I thus obtained which contains at least one chiral centre is resolved into its enantiomers.

41. A process as claimed in any one of claims 12 to 40 wherein a compound of general formula I as defined in claim 1 initially obtained is subsequently converted into an acid addition salt thereof or an acid addition salt of a compound of general formula I initially obtained is subsequently converted into a compound of general formula I.

42. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

43. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 13.

44. Compounds as claimed in claim 1 whenever

prepared by a process as claimed in any one of claims 12 to 43.

45. Pharmaceutical compositions containing, as active ingredient, at least one compound of general formula I as defined in claim 1, or a physiologically acceptable acid addition salt thereof, in association with one or more pharmaceutical carriers or excipients.

46. Compositions as claimed in claim 45 in the form of dosage units.

47. Compositions as claimed in claim 45 or claim 46 in the form of plain or coated tablets, powders, suppositories, suspensions, drops or ampoules.

48. Compositions as claimed in claim 45 substantially as herein described.

49. Compositions as claimed in claim 45 substantially as herein described in any one of Examples I to V.

50. Pharmaceutical compositions suitable for the treatment of central nervous, neuropsychiatric diseases, particularly schizophrenia, Parkinsonism or Parkinson's disease and/or circulatory disorders, particularly hypertension, containing as active ingredient an effective amount of a compound of general formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof.

For the Applicants
DR. REINHOLD COHN AND PARTNERS
By:

68072/PC/jg/pcc